General

Guideline Title

Use of imaging in multiple sclerosis.

Bibliographic Source(s)

Filippi M, Rocca A, Arnold DL, Bakshi R, Barkhof F, De Stefano N, Fazekas F, Frohman E, Miller DH, Wolinsky JS. Use of imaging in multiple sclerosis. In: Gilhus NE, Barnes MP, Brainin M, editor(s). European handbook of neurological management. 2nd ed. Vol. 1. Oxford (UK): Wiley-Blackwell; 2011. p. 35-51. [176 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Filippi M, Rocca MA, Arnold DL, Bakshi R, Barkhof F, De Stefano N, Fazekas F, Frohman E, Wolinsky JS. EFNS guidelines on the use of neuroimaging in the management of multiple sclerosis. Eur J Neurol 2006 Apr;13(4):313-25.

Recommendations

Major Recommendations

The levels of evidence (Class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good Clinical Practice Point [GCPP]) are defined at the end of the "Major Recommendations" field.

Magnetic Resonance Imaging (MRI) Assessment of Patients at Presentation with Clinically Isolated Syndromes (CIS) Suggestive of Multiple Sclerosis (MS)

In patients at presentation with CIS suggestive of MS (i.e., neurological findings typically seen in the setting of MS) after appropriate exclusion of alternative diagnostic considerations that can mimic MS, the following recommendations should be considered:

1. Conventional MRI (cMRI) of the brain (dual-echo, fluid attenuated inversion recovery [FLAIR] and post-contrast T1-weighted scans) should be obtained as soon as possible in all patients presenting with an isolated demyelinating syndrome involving the central nervous system (CNS), not only to collect additional evidence for disease dissemination in space (DIS), but also to exclude other possible neurological conditions. As suggested by recent guidelines from the American Academy of Neurology (Frohman et al., 2003) the finding in these patients of three or more T2-hyperintense lesions with the imaging characteristics underlined by the International Panel (IP) guidelines (McDonald et al., 2001; Polman et al., 2005) (Level A recommendation) and the presence of two or more gadolinium (Gd)-enhancing lesions at baseline are sensitive predictors of the subsequent development of clinically definite MS (CDMS) within the next 7 to 10 years (Level B recommendation).
2. The presence of three or more white matter (WM) lesions on brain T2-weighted MRI in patients suspected of having MS is not diagnostic,

especially when their location and appearance is non-characteristic for demyelination. In this context the IP criteria (McDonald et al., 2001; Polman et al., 2005) should be applied. Incidental WM lesions are not an infrequent observation even in the young normal population. Note that with ageing (at least >50 years) incidental WM lesions may also show progression (Longstreth et al., 2005) (GCPP).

3. In the case of corticosteroid treatment, which is known to dramatically suppress Gd enhancement, one of the possible markers of inflammation, cMRI should be performed before treatment or, at least, 1 month after treatment termination (GCPP).
4. cMRI of the spinal cord is useful in those circumstances when brain MRI is normal or equivocal, and in patients with non-specific brain T2-abnormalities (especially when older than 50 years), because, contrary to what happens for the brain, cord lesions rarely develop with ageing *per se* (Kidd et al., 1993). In patients presenting with a spinal cord syndrome, spinal cord MRI is highly recommended to rule out other conditions that may mimic MS, such as compressive lesions (GCPP).
5. In patients with acute optic neuritis (ON), although it will not always be required, MRI of the optic nerve can be useful in ruling out alternative diagnosis. In this case, short-tau inversion recovery (STIR) sequences should be used (GCPP).
6. Follow-up MRIs are required to demonstrate disease dissemination in time (DIT). In this perspective, the appearance of Gd-enhancing lesions 3 months after the clinical episode or new T2 or Gd-enhancing lesions 30 days after the clinical episode (and after a baseline MRI assessment) is highly predictive. Follow-up scans should be performed with the same machinery and scanning parameters and identical slice positions are required for exact comparison (Level B recommendation). A scanner with at least 1.0 Tesla should be used to optimize image quality and tissue contrast.
7. Repeat scanning beyond the two initial studies need to be considered by the neurologist individually according to the clinical circumstances that are appropriate for each patient (is not routinely recommended as the disease becomes more likely to manifest clinically in the longer term [Miller et al., 2004]) (GCPP).
8. Nephrogenic systemic fibrosis (NSF) is a medical condition that has come to be associated with exposure to the Gd (Kanal et al., 2007; Thomsen & European Society of Urogenital Radiology, 2007). Normal renal function has to be confirmed prior to Gd administration (GCPP).
9. Although non-conventional MRI techniques may provide essential and critical information in patients with CIS and their application for monitoring treatment might provide a more accurate assessment of efficacy on inflammation, axonal protection, and demyelination/remyelination, their use in clinical practice is, currently, not recommended. All these techniques are yet to be adequately compared with cMRI for sensitivity and specificity in detecting tissue damage in MS and for predicting the development of MS and disability. At present, these quantitative techniques show differences at a group level, but do not allow inferences at an individual level (GCPP).
10. In patients with insidious neurological progression over at least one year, primary-progressive MS (PPMS) (Thompson et al., 2000), can be diagnosed reliably in the absence of positive cerebrospinal (CSF) findings (when typical brain and spinal cord MRI changes are present). Even if in these patients a positive CSF finding increases the level of confidence for a diagnosis of MS, such a finding is not specific and may be commonly detected in patients with progressive myelopathies of other causes (GCPP).

MRI in Patients with CDMS

In patients with established MS, the following recommendations should be considered:

1. cMRI scans (dual-echo and post-contrast T1-weighted images) should be obtained using standardized protocols and accurate procedures for patients' repositioning to facilitate the interpretation of follow-up studies. Post-contrast T1-weighted scans should be acquired after an interval of 5 to 7 min from the injection of contrast material. Considering the weak correlation with clinical finding and the low predictive value of cMRI metrics for the subsequent worsening of clinical disability, the use of surveillance MRI for the purpose of making treatment decisions cannot be generally recommended. Serial MRI scans should be considered when diagnostic issues arise (GCPP).
2. Repetition of MRI of the spinal cord is advisable only if suspicion arises concerning the evolution of an alternate process (e.g., mechanical compression) or atypical symptoms develop (GCPP).
3. Although preliminary work based on clinical trial data has suggested that presence and amount of MRI-detected disease activity may identify interferon (IFN) response status in terms of relapse rate and accumulated disability in MS patients at a group level, there are no validated methods for monitoring disease-modifying therapy in individual patients (Class I evidence).
4. Metrics derived from cMRI are not enough to provide a complete picture of the MS pathological process. Although cMRI has undoubtedly improved our ability to assess the efficacy of experimental MS therapies and, at least partially, our understanding of MS evolution, it provides only limited information on MS pathology in terms of accuracy and specificity and it has limited correlations with clinical metrics. This implies that the ability of a given treatment to modify metrics derived from cMRI does not mean that the treatment will necessarily be able to prevent the progressive accumulation of clinical disability, especially at an individual patient level.
5. Measurements of T1-hypointense lesions loads and brain and cord atrophy in clinical practice continue to be considered at a preliminary stage of development, as they need to be standardized in terms of acquisition and post-processing. Conversely, these metrics should be included as an end-point in disease-modifying agents trials to further elucidate the mechanisms responsible for disability (GCPP).

6. The application of non-conventional MRI techniques in monitoring patients with established MS in clinical practice is, at the moment, not advisable. All these techniques still need to be evaluated for sensitivity and specificity in detecting tissue damage in MS and its changes over time (GCPP).
7. Magnetization transfer (MT)-MRI should be incorporated into new clinical trials to gain additional insights into disease pathophysiology and into the value of this technique in the assessment of MS (Class II evidence). The performance and contribution of diffusion tensor MRI (DT-MRI) and MR spectroscopy (^{1}H-MRS) in multicenter trials still have to be evaluated.

Definitions:

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Rating of Recommendations

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Good Clinical Practice Point Where there was lack of evidence but consensus was clear the Task Force members have stated their opinion as good clinical practice points.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Multiple sclerosis (MS)

Guideline Category

Diagnosis

Evaluation

Technology Assessment

Clinical Specialty

Family Practice

Internal Medicine

Neurology

Radiology

Intended Users

Physicians

Guideline Objective(s)

- To define guidelines for the application of conventional and non-conventional magnetic resonance (MR) techniques for the diagnosis and monitoring of patients with multiple sclerosis (MS) in clinical practice
- To review the current status and clinical role of non-conventional MR techniques
- To update and revise previous guidelines published in 2006

Target Population

Patients with multiple sclerosis (MS) or suspected to have MS

Interventions and Practices Considered

Conventional magnetic resonance imaging (cMRI) of the brain

Note: Non-conventional MRI techniques (such as magnetization transfer MRI [MT-MRI], diffusion weighted MRI (DW-MRI); functional MRI [fMRI], and MR spectroscopy) were considered but not recommended.

Major Outcomes Considered

Sensitivity, specificity and predictive value of conventional magnetic resonance imaging (cMRI) in the management of multiple sclerosis (MS) patients

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Data for this review were identified by searches of Medline and references from relevant articles from 1965 to August 2009. The search terms 'multiple sclerosis', 'magnetic resonance imaging', 'diagnosis', 'prognosis', 'atrophy', 'magnetization transfer MRI', 'diffusion weighted MRI', 'diffusion tensor MRI', 'proton magnetic resonance spectroscopy', 'disability', and 'treatment' were used. Only papers published in English were reviewed.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Not stated

Rating Scheme for the Strength of the Recommendations

Rating of Recommendations

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Good Clinical Practice Point Where there was lack of evidence but consensus was clear the task force members have stated their opinion as Good Clinical Practice Points.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see the "Availability of Companion Document" field).

Evidence Supporting the Recommendations

References Supporting the Recommendations

Frohman EM, Goodin DS, Calabresi PA, Corboy JR, Coyle PK, Filippi M, Frank JA, Galetta SL, Grossman RI, Hawker K, Kachuck NJ, Levin MC, Phillips JT, Racke MK, Rivera VM, Stuart WH. The utility of MRI in suspected MS: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2003 Sep 9;61(5):602-11. [47 references] PubMed

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Thompson AJ, Montalban X, Barkhof F, Brochet B, Filippi M, Miller DH, Polman CH, Stevenson VL, McDonald WI. Diagnostic criteria for primary progressive multiple sclerosis: a position paper. Ann Neurol. 2000 Jun;47(6):831-5. PubMed

Thomsen HS, European Society of Urogenital Radiology. European Society of Urogenital Radiology guidelines on contrast media application. Curr Opin Urol. 2007 Jan;17(1):70-6. [58 references] PubMed

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for selected recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of neuroimaging in the management of multiple sclerosis (MS)

Potential Harms

Nephrogenic systemic fibrosis (NSF) is a medical condition that has come to be associated with exposure to gadolinium (Gd). Normal renal function has to be confirmed prior to Gd administration.

Qualifying Statements

Qualifying Statements

This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

Implementation of the Guideline

Description of Implementation Strategy

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2006 Apr (revised 2011)

Guideline Developer(s)

European Academy of Neurology - Medical Specialty Society

Source(s) of Funding

European Federation of Neurological Societies

Guideline Committee

European Federation of Neurological Societies Task Force on Use of Imaging in the Multiple Sclerosis

Composition of Group That Authored the Guideline

Task Force Members: M. Filippi, Institute of Experimental Neurology, Scientific Institute and University Ospedale San Raffaele, Milan, Italy; M. A. Rocca, Institute of Experimental Neurology, Scientific Institute and University Ospedale San Raffaele, Milan, Italy; D. L. Arnold, Montreal Neurological Institute, Canada; R. Bakshi, Partners MS Center, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; F. Barkhof, VU Medical Centre, Amsterdam, The Netherlands; N. De Stefano, Institute of Neurological Sciences, University of Siena, Italy; F. Fazekas, Institute of Neurological Sciences, University of Siena, Italy; E. Frohman, University of Texas Southwestern Medical Center at Dallas, USA; D. H. Miller, Institute of Neurology, Queen Square, London, UK; J. S. Wolinsky, University of Texas Health Science Center, Houston, USA

Financial Disclosures/Conflicts of Interest

D. L. Arnold has served on advisory boards for Genentech and Biogen Idec, and received speaker honoraria from Genentech, MS Forum, Biogen Idec, Serono Symposia, Teva & Sanofi Aventis, Teva Neuroscience, Bayer HealthCare Pharmaceuticals, and EMD Serono. He has received consultant's fees from Biogen Idec, Teva Neuroscience, MS Forum, Genentech, Bayer HealthCare Pharmaceuticals, Novartis, and Eisai

Medical Research, and grants from Multiple Sclerosis Society of Canada and Canadian Institutes of Health Research.

R. Bakshi has received speaker honoraria and grants from Biogen Idec, Teva Neuroscience, and EMD Serono.

F. Barkhof has received consultancy fees from Bayer-Schering Pharma, Sanofi-Aventis, Biogen-Idec, UCB, Merck-Serono, Novartis, and Roche.

N. De Stefano has served on advisory boards for Merck-Serono and received speaker honoraria from Merck-Serono, Teva, Biogen, and Bayer. He has received a consultant's fee from Merck-Serono and travel grants from Merck-Serono and Biogen.

F. Fazekas has served on advisory boards and received speaker honoraria from Biogen Idec, Teva Sanofi Aventis, Merck-Serono, and Bayer Schering. He has received grants from Bayer Schering, Biogen Idec, Teva Sanofi-Aventis, Baxter, and Merck-Serono.

M. Filippi has received speaker honoraria and grants from Teva, Merck-Serono, Bayer Schering, Biogen-Dompè, and Genmab. He has received a consultant's fee from Pepgen and travel grants from Teva, Merck-Serono, Bayer Schering, and Biogen-Dompè.

M. A. Rocca has received speaker honoraria and travel grants from Biogen-Dompè.

The other authors have reported no conflicts of interest.

Guideline Status

This is the current release of the guideline.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies (EFNS) Web site .

Availability of Companion Documents

The following is available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on March 20, 2007. The information was verified by the guideline developer on May 3, 2007. This summary was updated by ECRI Institute on June 20, 2007 following the U.S. Food and Drug Administration (FDA) advisory on gadolinium-based contrast agents. This summary was updated by ECRI Institute on January 13, 2011 following the U.S. Food and Drug Administration (FDA) advisory on gadolinium-based contrast agents. This NGC summary was updated by ECRI Institute on February 20, 2012.

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